

Physiological Differences and Similarities in Asthma and COPD—Based on Respiratory Function Testing—

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ABSTRACT

Physiological differences and similarities in asthma and COPD are documented based on respiratory function testing. (1) The airflow reversibility is usually important for the diagnosis of asthma. However, patients with long disease histories may have poor reversibility. The reversibility test in COPD is useful for predicting the treatment response. (2) In some of the stable asthmatic patients without attack, the concave downslope of flow-volume curve is present. In severe COPD, the flow in the second half of the curve is smaller than that of rest-breathing. (3) Inspiratory capacity (IC) is a good estimator of air trapping and of predicting the exercise capacity in COPD or persistent asthma. (4) Peak expiratory flow (PEF) can be an important aid in both diagnosis and monitoring of asthma. PEF is not used in COPD because the main disorder is in the peripheral airway. (5) Measurements of airway responsiveness may help to a diagnosis of asthma. However, many COPD cases also have it. (6) Impulse oscillation system (IOS) revealed that the predominant airway disorders in asthma and COPD are central and peripheral respiratory resistance, respectively. However, some asthma patients have larger values of peripheral component. (7) DLCO reflects the extent of pathological emphysema and it is useful for the follow-up of COPD, whereas DLCO is not decreased in asthma. (8) The patient with widened A-aDO₂ and alveolar hypoventilation may lead to the life threatening hypoxia in severe asthma attack or severe COPD. When PaCO₂ overcomes PaO₂, the patient should immediately be treated by mechanical ventilation.

KEY WORDS

airflow reversibility, airway responsiveness, diffusion capacity, flow-volume curve, impulse oscillation system

INTRODUCTION

The physiological measurements of asthma and COPD are considered to be indispensable tools to differentiate these diseases and maintain an up-to-date knowledge of the disease condition. The present review will clarify the physiological differences and similarities between asthma and COPD based on respiratory function testing, mainly according to GINA-2007 (Global Strategy for Asthma Management and Prevention) and GOLD-2008 (Global Initiative for Chronic Obstructive Lung Disease).^{1,2}

SPIROMETRY

The most characteristic feature of the lung function during an asthma attack and COPD is the airflow limitation. During an asthma attack, the airway lumen becomes narrow due to airway smooth muscle (ASM) contraction, mucosal edema and accumulation of sputum. The airflow limitation is usually reversible. However, in many cases with long disease histories, the airflow limitation is irreversible due to airway remodeling. In COPD, the airflow limitation is chronic and irreversible. It is caused by airway inflammation mainly in peripheral lesions (bronchitis) and by parenchymal destruction (emphysema), although the

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Received 9 June 2009.
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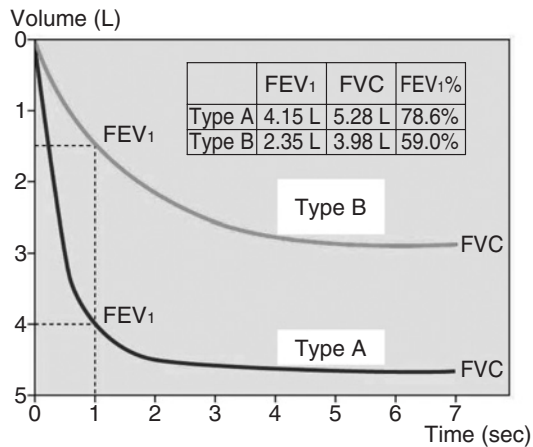


Fig. 1 Normal spirogram and spirogram typical of patients with asthma during moderate attack or moderate COPD (ref-2). Type A: Normal. Type B: Asthma during moderate attack or moderate COPD.

relative contributions of these factors vary from person to person. An indispensable measurement to detect airflow limitation is spirometry. The subject is usually asked to expire with maximum effort from the maximum inspiratory level (TLC: total lung capacity) to the maximum expiratory (RV: residual volume) level. There are two ways of analyzing the data: (1) volume (Y axis)-time (X axis) curve, (2) flow (Y axis)-volume (X axis) curve. Both of these methods are informative for estimating the condition of asthma and COPD.

VOLUME-TIME CURVE (FIG. 1)

The expired volume measured from the beginning to the end of the forced expiratory maneuver is defined as FVC (forced expiratory volume). Asthma and COPD patients usually have normal FVC values. However, the airways collapse when an expiratory volume has been reached close to the level of the residual volume, at which stage the airflow limitation becomes severe, and therefore FVC is decreased. This situation leads to the “restrictive ventilatory disorder coupled with severe obstructive disorder”. The expired volume during the initial one second is defined as FEV₁, %FEV₁ is defined as $100 \times \text{FEV}_1 / \text{pFEV}_1$, where pFEV₁ is the predicted normal value calculated based on gender, age and height. FEV₁% is defined as $100 \times \text{FEV}_1 / \text{FVC}$, and obstructive ventilatory disorder is defined as “FEV₁% < 70%”. In asthmatic patients, obstructive ventilatory disorder during an asthma attack is usually reversible, and is completely rescued by bronchodilators. However, patients with a long disease history have irreversible obstructive disorder due to airway remodeling. Furthermore, asthmatic patients with a history of smoking may have irreversible obstructive disorder due to the comorbidity of COPD. “FEV₁% < 70% after bronchodilators” is

necessary for defining COPD. Accordingly, the stage of COPD is defined from %FEV₁, where 30%, 50% and 80% are the boundary values for the staging; I (mild), II (moderate), III (severe), IV (very severe). FEV₁% is not used in the staging of COPD. FEV₁% (=FEV₁/FVC) does not adequately reflect the airflow limitation in severe COPD because FVC as well as FEV₁ are decreased in severe COPD. The same limitation is present for asthmatic patients. %FEV₁ is a better estimator of airflow limitation than FEV₁%.

The bronchodilator reversibility is defined as an increase in FEV₁ that is both greater than 200 ml and 12% above the pre-bronchodilator FEV₁.³ This means that the 200 ml criterion is adopted in cases of pre-bronchodilator FEV₁ less than 1,666 ml, and that the 12% criterion is adopted in cases with FEV₁ greater than 1,666 ml. In asthma, a β_2 -agonist is usually used as a bronchodilator. The airflow reversibility is important for the diagnosis of asthma. However, patients with long disease histories may have poor reversibility. In COPD, a β_2 -agonist or an anticholinergic agent, or a combination of the two, is used. Despite earlier hopes, neither bronchodilator reversibility nor corticosteroid reversibility testing predicts disease progression, whether judged by a decline in FEV₁, deterioration of health status, or frequency of exacerbations.⁴ Minor variations in initial airway caliber can lead to different classifications of reversibility status depending on the day of testing, and the lower the pre-bronchodilator FEV₁, the greater the chance of a patient being classified as reversible, even when the 200 ml criterion is included. However, the reversibility test is useful for predicting the treatment response and is diagnostic for some cases, for example, in patients with atypical histories, such as asthma in childhood and regular night waking with cough or wheeze.

FLOW-VOLUME CURVE (FIG. 2)

The characteristics of the flow-volume curve are as follows; (1) The flow of the first half of the downslope reflects the condition of central and peripheral airways, and the flow of the second half reflects the condition of peripheral airways. (2) The second half of the downslope is effort independent. Figure 2 shows representative curves of asthma without attack (FEV₁% = 72.0%, %FEV₁ = 82.0%) (A) and severe COPD (FEV₁% = 42.0%, %FEV₁ = 28.2%) (B). The dotted linear downslopes represent normal curves. Even in the attack-free condition in the asthmatic patients, the flow is decreased at the beginning of the downslope, and the second half of the curve shows a straight line (Fig. 2A). These findings are derived from central airway flow limitations during the forced expiratory maneuver, and are useful for making a diagnosis in the attack-free asthma. In COPD, the peak expiratory flow is very low, and the downslope of the curve is concave because of the severe airflow limita-

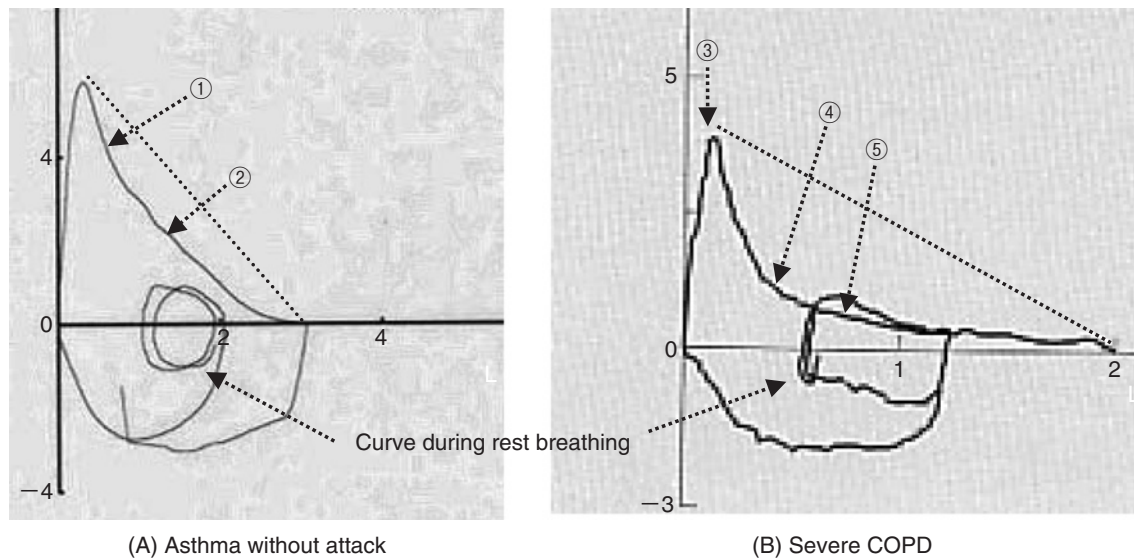


Fig. 2 Flow-volume curve typical of patients with asthma without attack (A) and severe COPD (B). ① Decreased flow at the beginning of downslope, ② Straight line, ③ Decreased peak flow, ④ Concave line, ⑤ Flow less than that of rest breathing.

tion in the peripheral airway. The flow limitation in the peripheral airway in COPD is due to the following two factors; (1) increased peripheral airway resistance due to remodeling, (2) airway collapse during the expiratory effort due to the decreased parenchymal tethering. Parenchymal tethering is the supportive force of the lung tissue that keeps the airway lumen open, and it is decreased by the destruction of the lung tissue seen in, for example, emphysema. In some of the stable asthmatic patients without asthma attack the concave downslope is present. This may be informative in clarifying the remodeling of the peripheral airways in asthma. In some of the patients with severe COPD, the flow in the second half of the curve is smaller than that of rest-breathing (Fig. 2B). This finding shows that the expiratory effort makes the peripheral airway collapse, and this indicates that the airways are extremely collapsible and that the condition is extremely severe.

For the quantification of the downslope of the flow-volume curve, V'_{25} and V'_{50} have been adopted. V'_{25} and V'_{50} are flow rates at the lung volume of RV (residual volume) plus $VC \times 0.25$ and $VC \times 0.5$, respectively. A V'_{25} value less than $0.8 \times$ predicted V'_{25} and ($V'_{50}/V'_{25} > 3.0$) has been used as the criteria indicating an airflow limitation in the peripheral airway. However, the value of V'_{25} has been reported to be too small to provide reliable data. Recently, $FEF_{25-75\%}$ (mean forced expiratory volume from 25% to 75% VC from RV) has been used as an indicator of the peripheral airway condition. However, it should be reminded that $FEF_{25-75\%}$ is also highly affected by the large airway condition.

LUNG VOLUME

The lung volume is composed of four elements: IRV (inspiratory reserve volume), TV (tidal volume), ERV (expiratory volume) and RV (residual volume). Four kinds of lung capacity are defined from the complex of the elements: IC (inspiratory capacity: $IRV + TV$), FRC (functional residual capacity: $ERV + RV$), VC (vital capacity: $IRV + TV + ERV$) and TLC (total lung capacity: $IRV + TV + ERV + RV$). FRC, VC and TLC cannot be measured by spirometry because they include RV. There are two ways of measuring RV: The gas dilution method and the body plethysmographic method. The gas dilution method (He dilution or N_2 wash-out method) does not estimate the poorly ventilated air space. In contrast, the body plethysmographic method estimates all of the airspace in the lung because the lung volume is calculated from the volume change induced by compression of the thoracic wall. Thus, the difference in volume measured by the two methods equals the poorly ventilated air space, which increases in COPD with emphysema.

In COPD, TLC is increased because of hyperinflation of the lung, and RV is also increased because of collapse of the peripheral airway in the early expiratory phase. However, the increase of RV overcomes the increase of TLV, and VC and IC are decreased. Thus, the severe COPD patient has both obstructive and restrictive ventilatory impairment. Recently, "air trapping" has been a topic of discussion. TV must be increased during exercise, but complete expiration is difficult in advanced COPD because of the airflow limitation, resulting in an increase of ERV and a decrease of IC. This situation makes it difficult to in-

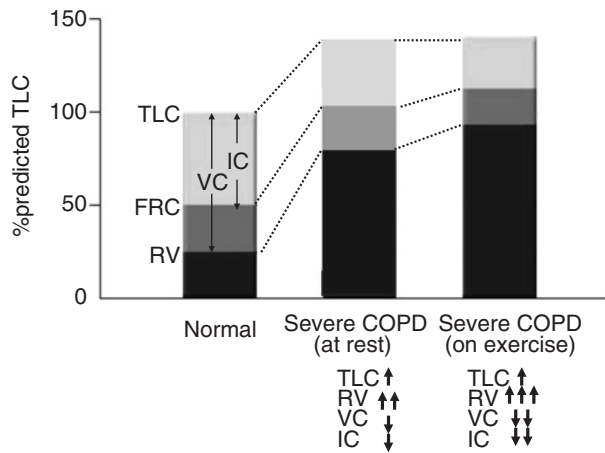


Fig. 3 Lung volume in COPD at rest or during [on] exercise. ① VC and IC are decreased due to the increase of RV. ② These phenomena are amplified by exercise. ③ These phenomena may also be noted in persistent asthma.

crease ventilation and becomes the cause of dyspnea during exercise. IC is reported to be a good estimator of air trapping and of predicting the exercise capacity in COPD⁵ (Fig. 3).

All of these findings in lung volume cannot usually be applied to asthma in the stable condition. However, in patients with persistent asthma or asthma with a long history, similar findings may be obtained, such as an increase of RV and decreases of VC and IC due to the peripheral airway flow limitation.

PEAK EXPIRATORY FLOW (PEF)

PEF measurements are made using a peak flow meter, and it can be an important aid in both diagnosis and monitoring of asthma, but PEF is not used in COPD because the main airway disorder of COPD is in the peripheral airway. Modern PEF meters are relatively inexpensive, portable, and ideal for patients to use in home settings for day-to-day objective measurements of airflow limitation. The clinical use of PEF in asthma is as follows: (1) To confirm the diagnosis of asthma. Although spirometry is the preferred method of documenting airflow limitation, a 60 L/min (or 20% or more of prebronchodilator PEF) improvement after inhalation of a bronchodilator, or diurnal variations in PEF of more than 20% (with twice daily readings, more than 10%) suggests a diagnosis of asthma. (2) To improve control of asthma, particularly in patients with poor perception of symptoms. Asthma management plans that include self-monitoring of symptoms or PEF for treatment of exacerbations have been shown to improve asthma outcomes. It is easier to discern the response to therapy from a PEF chart than from a PEF diary, provided the same chart format is consistently used.⁶ (3) To identify environmental (including occupational) causes of asthma symptoms. This involves the patient monitor-

ing PEF daily or several times each day over periods of suspected exposure to risk factors in the home or workplace, or during exercise or other activities that may cause symptoms, and during periods of non-exposure.

However, measurements of PEF are not interchangeable with other measurements of lung function such as FEV₁ in either adults⁷ or children.⁸ PEF can underestimate the degree of airflow limitation, particularly as airflow limitation and gas trapping worsen. Because values for PEF obtained with different peak flow meters vary and the range of predicted values is too wide, PEF measurements should preferably be compared to the patient's own previous best measurements using his/her own peak flow meter.⁹ One method of describing diurnal PEF variability is as the amplitude (the difference between the maximum and minimum values for the day), expressed as a percentage of the mean daily PEF value. Another method of describing PEF variability is by recording the minimum morning pre-bronchodilator PEF over 1 week, expressed as a percent of the recent best PEF value (Min%Max) (Fig. 4). This latter method has been suggested to be the best PEF index of airway lability for clinical practice because it requires only a once-daily reading, correlates better than any other index with airway hyperresponsiveness, and involves only a simple calculation.

MEASUREMENT OF AIRWAY RESPONSIVENESS

For patients with symptoms consistent with asthma, but with normal lung function, measurements of airway responsiveness to direct airway challenges such as inhaled methacholine and histamine or indirect airway challenges such as inhaled mannitol or exercise challenge may help establish a diagnosis of asthma.¹⁰ Two methods are used for the measurement. One is a traditional method using FEV₁. The test results are usually expressed as the provocative concentration (or dose) of the agonist causing a given fall (often 20%) in FEV₁. However, this measurement is applied only to patients who can perform a forced expiratory maneuver, and the repeated forced expiration may change lung mechanics. Another procedure is a forced oscillation method, which measures the change in respiratory resistance (Rrs) to a 3 Hz sinusoidal pressure wave driven from the mouth during rest-breathing. The provocative dose of the agonist causing an initial increase in Rrs is defined as the "sensitivity", and the rate of increase of the Rrs is defined as the "specificity".¹¹ The forced oscillation method has the advantage that it can be applied to children or elderly patients who find it difficult to perform forced expiration.

These tests are sensitive for making a diagnosis of asthma, but have limited specificity.¹² This means that a negative test can be useful to exclude a diagno-

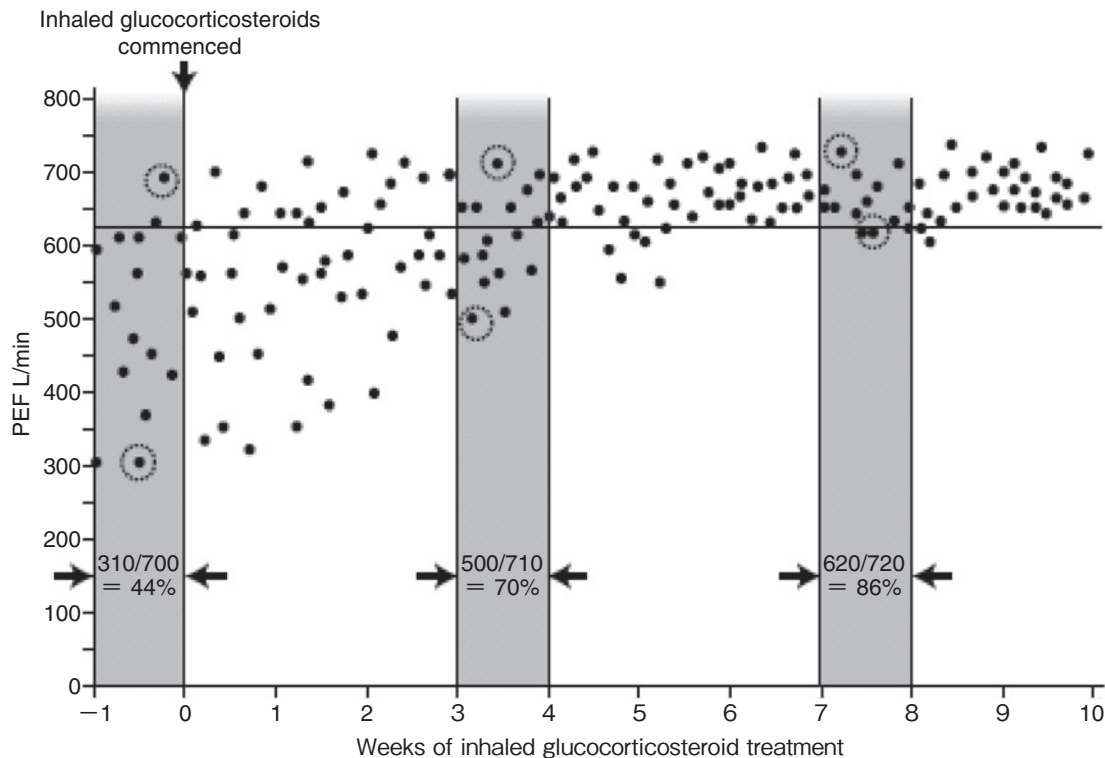


Fig. 4 Measuring PEF variability in asthma (Ref-1). PEF chart of a 27-year-old man with long-standing, poorly controlled asthma, before and after the start of inhaled glucocorticosteroid treatment. With treatment, PEF levels increased, and PEF variability decreased, as seen by the increase in Min% Max (lowest morning PEF/highest PEF%) over 1 week.

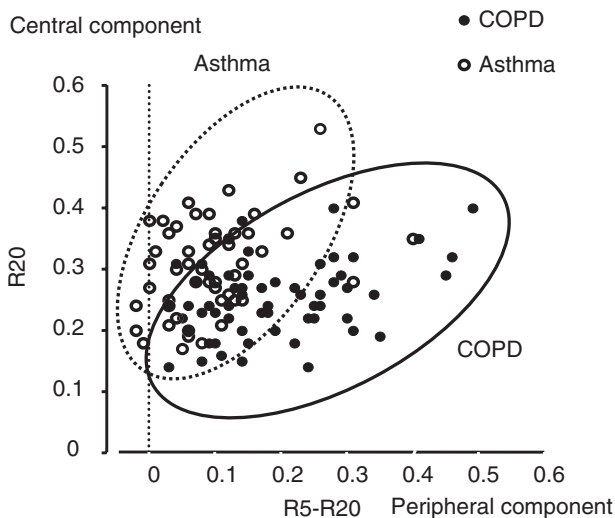


Fig. 5 Relationship between central (R20) and peripheral component (R5-R20) of respiratory resistance in asthma and COPD (Ref-16).

sis of persistent asthma in a patient who is not taking inhaled glucocorticosteroid treatment, but a positive test does not always mean that a patient has asthma. This is because airway hyperresponsiveness has

been described in patients with allergic rhinitis¹³ and in those with airflow limitations caused by conditions other than asthma, such as COPD.¹⁴

IMPULSE OSCILLATION SYSTEM (IOS)

IOS is a type of oscillation mechanics. Impulse pressure waves ranging from 0 to 100 Hz are loaded from the mouth of subjects during rest-breathing, and frequency characteristics of the respiratory impedance are calculated from the pressure and flow.¹⁵ The real part of the impedance at low frequency: 5 Hz (R5) and high frequency: 20 Hz (R20) are approximated to reflect the total and distal components of the respiratory resistance, and R5-R20 is approximated to be the peripheral component. Figure 5 shows the relationship between R5 (central component) and R5-R20 (peripheral component) in asthma—with the smaller FEV₁ predicted to be less than 80%—and COPD. The results suggest that the predominant airway disorders in asthma and COPD are central and peripheral, respectively.¹⁶ However, some asthma patients have larger values of R5-R20, which means that the peripheral airway disturbance is also important for the control of asthma. A comparison of the aerosol size of the corticosteroid inhalation agent relative to its therapeutic effect on asthma is shown in Figure 6.¹⁷ The

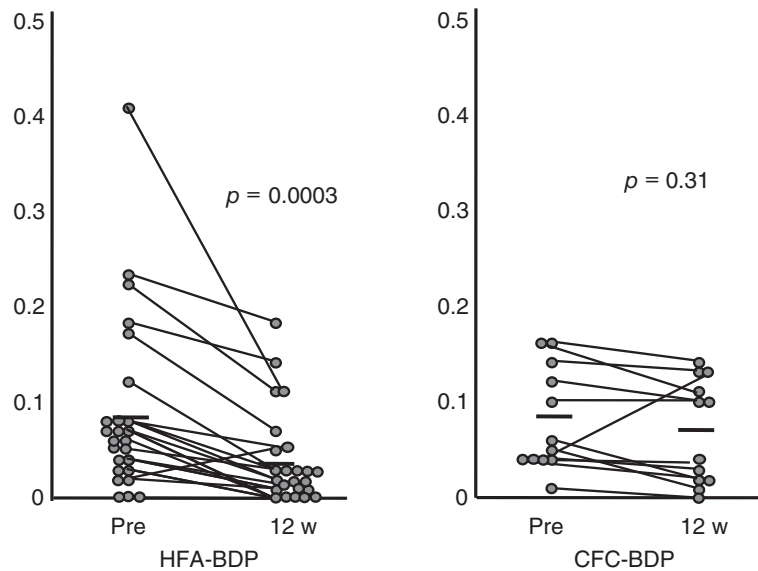


Fig. 6 Effect of treatment on peripheral component (R5-R20) of respiratory resistance (Ref-17). $p = 0.044$ between the treatments. Inhalation of the smaller size aerosol (HFA-BDP) has more effective than the larger size (CFC-BDP) to improve R5-R20 (peripheral component).

Table 1

	PaO ₂ = 150 - PaCO ₂ /0.8 - AaDO ₂				
Type	A	B	C	D	E
PaCO ₂	40	80↑	40	32	80↑
AaDO ₂	10	10	40↑	40↑	40↑
PaO ₂	90	40↓	60↓	70↘	10↓↓
	mmHg				

12-week inhalation of the smaller-size aerosol (HFA-BDP) was more effective than the inhalation of larger sizes (CFC-BDP) in improving R5-R20 (peripheral component). As to the treatment of COPD, R5 is useful in estimating the effect of muscarinic M2 receptor inhibitor on the airway obstruction of COPD due to the inhalation of dry cold air.¹⁸

IOS is an examination that is not dependent on effort, and it can be applied to children or old persons who find it difficult to perform a forced expiratory maneuver.¹⁹ IOS has the additional advantage that it can measure the central and peripheral components of respiratory impedance separately. One must be careful and realize that R5 and R5-R20 are not equal to central and peripheral airway resistance, respectively. Both parameters include the influence of the lung tissue - chest wall impedance and the parallel inhomogeneity of ventilation.

DIFFUSION CAPACITY (DLCO)

DLCO is an estimator of the diffusion capacity of the lung using carbon monoxide. DLCO is calculated from the speed of reduction of alveolar CO density after a deep inspiration of CO (1%) and breath-holding (10

sec). The DLCO value is about the same as DL02, and it is easier to calculate than DL02 because the partial pressure of CO at the pulmonary capillary is negligible. The determinants of DLCO are (1) diffusion capacity between alveoli and alveolar capillary, (2) ventilation-perfusion distribution, (3) amount of the alveolar capillary bed, and (4) Hb (hemoglobin) density.

DLCO is reported to reflect the extent of pathological emphysema and it is an important index for the follow-up of COPD.²⁰ The decrease of DLCO in emphysema is explained as originating from the decrease of the capillary bed and the unevenness of ventilation-perfusion distribution. Hb density is an important factor to consider. Some COPD patients may have anemia due to their poor condition. In contrast, other patients may have a high Hb density because of their nocturnal hypoxia and resulting erythropoietin production. These situations may result in the underestimation or overestimation of the diffusion capacity. Thus DLCO must be corrected according to the Hb density using the following formula and assuming that the normal Hb density is 14.6 g/dl.;

Corrected DLCO = Measured DLCO × (10.22 + Hb)/1.7 Hb.

DLCO has been documented to be increased in asthma because of the increase of blood volume of the capillary bed due to the lung congestion. However, this may not always be the case because unevenness of the ventilation-perfusion distribution may cancel the increase of DLCO caused by the lung congestion in asthma.

ARTERIAL BLOOD GAS ANALYSIS (ABGA)

ABGA is the final output of the lung function, and the deterioration of ABG may be fatal. The A-aDO₂ (alveolar-arterial difference of oxygen) is important for assessing the current condition of the lungs, and it is calculated under the room air condition as follows:

$$A-aDO_2 = 150 - PaCO_2/0.8 - PaO_2 \text{ --- (A)}$$

where 150 is the O₂ pressure of the room air and 0.8 is a respiratory quotient.

The normal value of A-aDO₂ is less than 20 mmHg, which corresponds to PaCO₂ = 40 mmHg, PaO₂ = 80 mmHg. A ventilation-perfusion mismatch and/or a decrease of the diffusion capacity will widen the A-aDO₂. In the case of asthma, A-aDO₂ is easily widened by the ventilation-perfusion mismatch during an asthma attack because of the uneven bronchoconstriction. In the case of COPD, the decrease of the alveolar capillary bed due to emphysema may be additive to the airway narrowing; the ventilation-perfusion mismatch is highly variable, and the degree of A-aDO₂ widening varies considerably among patients.

Equation (A) can be transformed into (B) as follows:

$$PaO_2 = 150 - PaCO_2/0.8 - A-aDO_2 \text{ --- (B)}$$

Equation (B) is useful for understanding the mechanism of hypoxia, and 5 patterns are listed in Table 1. Pattern-A is that of normal subjects. PaCO₂ is reciprocally proportional to the alveolar ventilation, and a normal PaCO₂ value shows that alveolar ventilation is normal. A normal A-aDO₂ shows that a ventilation-perfusion mismatch or diffusion impediment does not exist. Thus, it is natural that PaO₂ calculated from equation (B) is normal. Pattern-B is that of neuromuscular disease. A-aDO₂ is normal (normal lung), but PaCO₂ is twice the normal value, which represents an alveolar ventilation that is half of the normal. These situations resulted in severe hypoxia. This situation cannot occur in asthma or COPD because alveolar hypoventilation is usually associated with ventilation-perfusion mismatch in asthma or COPD. Pattern-C, D, E are various patterns of asthma and COPD with widened A-aDO₂. Asthma during a mild-moderate attack or mild-moderate COPD usually has pattern C. However, patients who are sensitive to hypoxia and have a potential to increase alveolar ventilation, can show pattern D in an effort to overcome hypoxia (compensatory hyperventilation). However, the severe conditions of an asthma attack or severe COPD give rise to pattern-E, severe alveolar hypoventilation and severe hypoxia. The causes of hypercapnea (alveolar hypoventilation) in a severe asthma attack or severe COPD are (1) increase of physiological dead space, (2) increase of airway resistance and (3) muscle atrophy caused by steroid therapy or muscle fatigue. It must be realized that the stridor tends to be decreased during a severe asthma attack due to

the hypoventilation. The patient with widened A-aDO₂ and alveolar hypoventilation may succumb to the life threatening hypoxia. When PaCO₂ overcomes PaO₂, the patient should immediately be treated by mechanical ventilation.

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